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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,553	LU ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/14/04 has been entered.

Claims 1, 5-7 and 21 are pending.

Claims 1, 5-7 and 21 are under consideration in the instant application.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

3. Claim 1, 5-7 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite and ambiguous in recitation of "...introducing in vitro an agent that inhibits binding of LPAP and TIP-1 into a T cell..". It is unclear if an agent that inhibits binding of LPAP and TIP-1 is introduced into a T cells or an agent inhibits binding of LPAP and TIP-1 into a T cell ?

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 5-7 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

" A method of modulating T cell activation, comprising introducing in vitro an agent that inhibits binding of LPAP and TIP-1" claimed in Claim 1 represents a departure from the specification and the claims as originally filed. The passages pointed by the applicant do not provide a clear support for the method of modulating T cell activation, comprising introducing in vitro an agent that inhibits binding of LPAP and TIP-1". It is noted the term "modulating" claimed in claim 1, encompass both stimulation and inhibition of T cell activation . However, the Specification on page 129, lines 6-10 only generally disclosed that C-terminal core sequence of LPAP may be used to target a PDZ domain-containing protein to T cells and page 141, line 21-25 disclosed that inhibition of activation of T cells in vitro can be used for the evaluation of potential of PDZ/PL interaction antagonists. LPAP and TIP-1 pair is a subgenus of a genus of PDZ/PL pair. See *In re Smith* 173 USPQ 679, where it was ruled that a genus may not support a subgenus even though there is a disclosed species within the subgenus.

6. Also an issue is that Claims 1, 5-7 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

The claims as written encompass the genus of agent that inhibits binding of LAPA and TIP-1. The genus encompasses peptides or peptide mimetics wherein such peptides have numerous differences in amino acid sequences or small molecules.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant has not taught how to make and/or use *any* agent that inhibits binding of LAPA and TIP-1 as claimed in claim 1; or any peptide that is 4-25 or 12-25 amino acid in length and comprises a sequence of at least the carboxy-terminal two or three residues of LPAP as claimed in claims 5 , 6 and 21 , or any small molecule or any peptide mimetics of the carboxy-terminus LPAP, as claimed in claim 7 that can be used in a method of modulating T cell activation *in vitro*. The structural and functional characteristics of said peptides, small molecule or mimetics are not defined in the claim. Applicant has not provided sufficient biochemical information (e.g. structural characteristics, amino acid composition , physicochemical properties, etc) that distinctly identifies such *any* agent that inhibits binding of LAPA and TIP-1 as claimed in claim 1; or any peptide that is 4-25 or 12-25 amino acid in length and comprises a sequence of at least the carboxy-terminal two or three residues of LPAP as claimed in claims 5 , 6 and 21 , or

any small molecule or any peptide mimetics of the carboxy-terminus LPAP, as claimed in claim 7 . While "*any* agent that inhibits binding of LAPA and TIP-1 as claimed in claim 1; or any peptide that is 4-25 or 12-25 amino acid in length and comprises a sequence of at least the carboxy-terminal two or three residues of LPAP as claimed in claims 5 , 6 and 21 , or any small molecule or any peptide mimetics of the carboxy-terminus LPAP, as claimed in claim 7 may have some notion of the activity claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention.
Applicant has not enabled structurally related and unrelated *any* agent that inhibits binding of LAPA and TIP-1; or any peptide that is 4-25 or 12-25 amino acid in length and comprises a sequence of at least the carboxy-terminal two or three residues of LPAP, or any small molecule or any peptide mimetics of the carboxy-terminus LPAP, which would be expected to have difference in their activities to be used in the method of modulating T cell activation *in vitro*. Since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

"Comprising" is considered open-ended claim language and includes amino acid residues outside of the specified peptide. Therefore, a peptide "comprising" a sequence of least the carboxy-terminal two or three residues of LPAP includes an unlimited number of amino acid sequences "comprising" an unlimited number of polypeptides.

Protein chemistry is probably one of the most unpredictable areas of biotechnology . It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al., further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular). Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed peptides can be tolerated that will allow the protein to function as claimed, i.e. to inhibit LPAP and TIP-1 interaction. While it is known that many amino acid substitutions are possible in any given protein, the position within the

protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions.

Since the amino acid sequence of a polypeptide determined its structural and functional properties, predictability of which fragments will retain functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which structures would lead to functional proteins or peptides with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention. Without sufficient guidance, the changes which can be made in the structure of "*any* agent that inhibits binding of LAPA and TIP-1 as claimed in claim 1; or any peptide that is 4-25 or 12-25 amino acid in length and comprises a sequence of at least the carboxy-terminal two or three residues of LPAP as claimed in claims 5 , 6 and 21 , or any small molecule or any peptide mimetics of the carboxy-terminus LPAP, as claimed in claim 7 and still specifically blocks the interaction between LPAP and TIP-1 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

7. Also an issue that the specification does not indicate any function of LAPA and TIP-1 interaction in T cells activation.

Applicant's arguments, filed 1/14/04, have been fully considered, but have not been found convincing.

Applicant asserts that : (i) the specification does in fact ascribe a role for LPAP, noting that certain evidence indicates that LPAP is involved in the organization of a functional CD45 complex ; (ii) two submitted articles by Scraven et al and Bruyns et al. indicated that LPAP and CD45 associate non-covalently in T cells and that CD45 plays a role in lymphocyte activation.

Contrary to the Applicant's assertion, it is the examiner position that the specification does not teach the importance of LPAP /TIP-1 interaction in activation of T cell *in vitro*. The passage pointed by Applicant in the specification only stated that data obtained from LAPA deficient mice suggest that LPAP is an assembly molecule important for the organization of a functional CD45 complex. However, Applicant himself stated that at the time the invention was made the actual function of LPAP was unknown (see page 111, line 25 in particular). The references cited

by the Applicant only suggested that LPAP likely represent a substrate for CD45 and that LPAP might be protected from degradation through its interaction with CD45. However, none of the cited references teaches that LPAP/TIP-1 interaction are important for activation of T cell *in vitro*. Moreover, both articles sited by the Applicant clearly supported the Examiner position. For example, Bruyns et al., clearly stated that " the biological function of LPAP and its role in lymphocyte activation are unknown" (see page 31375 in particular). Similarly, Schraven et al., indicated that the biological role of LPAP remains to be elucidated (see page 29111 in particular).

Thus, since the function of LPAP is unknown (as disclosed on page 111, line 25 of the specification as filled and taught by Ding et al.; Bruyns et al., and Schraven et al.) how can one of ordinary skill in the art modulate T cell activation *in vitro* by an agent that inhibits binding of LPAP and TIP-1? Moreover, the exemplifications in the specification are drawn to general strategy that one would employ to identify an inhibitor for a particular PDZ/PL pair in *in vitro* assay "A" or assay G". There is no any *in vitro* data in the specification that shows modulation of T cell activation, comprising introducing an agent that inhibits LPAP/TIP-1 interaction. The specification does not adequately teach how to effectively modulate T-cell activation *in vitro* by introducing into the cell an agent that inhibits binding of LPAP with TIP1.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of modulating T cell activation *in vitro*, comprising introducing in vitro *any* agent that inhibits binding of LAPA and TIP-1; or any peptide that is 4-25 or 12-25 amino acid in length and comprises a sequence of at least the carboxy-terminal two or three residues of LPAP, or any small molecule or any peptide mimetics of the carboxy-terminus LPAP in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8 . Claims 1,5-7 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of a method of modulating T cell activation *in vitro*, comprising introducing in vitro *any* agent that inhibits binding of LAPA and TIP-1; or any peptide that is 4-25 or 12-25 amino acid in length and comprises a sequence of at least the carboxy-terminal two or three residues of LPAP, or any small molecule or any peptide mimetics of the carboxy-terminus LPAP

The claimed invention is drawn to a genus of agents that inhibits binding LPAP and TIP-1, however, structural identifying characteristics of the genus are not disclosed. There is no description of the identifying characteristics for recognizing that a candidate agent would inhibits binding LPAP and TIP-1. There is no evidence that there is any *per se* structure/function relationship between the disclosed agent compound and any others that might be found.

Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of what a material does rather than of what it is, usually does not suffice. The patent does not more than describe the desired function of the compound called for and contains no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work. Inadequate written description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived" *Fiers v. Revel*, 984 F.2d 1164,1171 9Fed.Cir. 1993).

A description of a genus of protein sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

9. No claim is allowed

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
March 8, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600